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Unbalanced t(4;11)(q32;q23) in a 34-Year-Old Man With Manifestations of Distal Monosomy 11q and Trisomy 4q Syndromes

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We present a 34-year-old man with an unbalanced translocation between the long arms of chromosome 4 and chromosome 11. He had manifestations of monosomy 11(q23)—minor facial anomalies, abnormal head shape, cryptorchidism; trisomy 4(q32)—hirsutism, renal disease; and manifestations attributable to both imbalances—heart disease, musculoskeletal anomalies, and mental retardation. FISH studies showed that the chromosome 11q23.3 translocation breakpoint was distal to the rare folate sensitive fragile site (FRA11B). The patient is the oldest reported with both imbalance of 4q+ and 11q–. Am. J. Med. Genet. 70:357–360, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: hirsutism; developmental delay; renal disease; congenital heart disease; FRA11B

INTRODUCTION

The 11q-syndrome was first described in 1973 in the unbalanced offspring of a family with a t(11;21) segregating in 4 generations [Jacobsen et al., 1973]. Subsequent reports [Monteleone et al., 1982; Sirota et al., 1984; Obregon et al., 1992; Stratton et al., 1994] and reviews [Fryns et al., 1987; Hustinx et al., 1993; Penny et al., 1995] expanded the phenotype. The smallest critical deletion interval may be due to loss of only one band—11q23–24, based on the overlapping regions of the deleted segment; but, in some cases the deleted segment is larger (from 11q23-qter) [Hustinx et al., 1993]. The syndrome comprises congenital heart disease, musculoskeletal anomalies, trigonocephaly, abnormal ears, and micrognathia. The manifestations of distal trisomy 4q include congenital heart disease, renal anomalies, musculoskeletal anomalies, bushy eyebrows, and minor facial anomalies, comprising slanting forehead, prominent nasal bridge, small mandible, downturned mouth, and deformed ears [Angulo et al., 1984; Zollino et al., 1995]. Some of these anomalies overlap with those of 11q–. Both conditions are associated with moderate intellectual handicap. Most cases of partial monosomy 11q are de novo in origin [Penny et al., 1995], whereas trisomy distal 4q is more frequently reported as the result of unbalanced chromosome rearrangements [Zollino et al., 1995].

Most cases of 11q– and 4q+ imbalances have been reported in infants and young children. The long term effects into adulthood are not well known. It was reported that females with 11q-syndrome survived longer than males [Monteleone et al., 1982]. We present a 34-year-old man with monosomy 11q and trisomy 4q. The patient is the oldest reported with either imbalance.

CLINICAL REPORT

The patient is the third living child of nonconsanguinous healthy parents, born by vaginal delivery at term, when the mother was 31 and the father 35 years old. There had been one miscarriage at 3 months, one son who had severe cardiac anomalies at birth and died at age 11 days, and 2 normal, healthy children. The pregnancy was complicated by first trimester bleeding. The patient was cyanosed at birth and needed oxygen resuscitation. His birth weight was 2.3 kg. He sucked poorly and failed to thrive. He had a congenital heart defect, consisting of a ventricular septal defect, ostium primum, pulmonary valve stenosis, and mild infundibular stenosis. He was markedly hypertonic in the arms and legs. The right testis was undescended and the left testis small. He had a triangular face and thin upper lip.

During infancy, he suffered repeated urinary tract infections, constipation, chronic cough, respiratory infections, and failure to thrive. The kidneys were abnormal, with bilateral hydronephrosis, dilation of both pel-

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vicalyceal systems, and horseshoe kidney malformation. The bladder and urethra were normal on cystogram. Congenital anomalies comprised a pidgeon chest deformity with asymmetry of the sternum to the left, gena valga, talipes equinovarus with high plantar arch and short foot, proximally placed thumbs, hypertelorism, external concomitant strabismus, low set ears, and accessory nipples. He had many hospital admissions and by age 14 years, surgery had been performed for congenital heart disease, renal anomalies, inguinal hernia, cryptorchidism, and several times for foot deformities.

At age 34 years his height was 163.3 cm (<3rd centile), weight 60.3 kg (10th–25th centile) and head circumference 58 cm (98th centile) with high bossed forehead and trigonocephalic skull shape. He had a high arched palate, enamel hypoplasia, "carp mouth," short neck, triangular face, narrow sloping shoulders, marked hirsutism of his limbs and trunk (Fig. 1), and numerous café-au lait spots were present (first detected at 20 years of age). He had residual marked abnormalities of his feet and wore built-up shoes. Residual abnormalities of the renal system included reflux nephropathy with persistent proteinuria and raised blood urea and serum creatinine levels, indicating slowly progressing renal insufficiency.

Development was delayed from the outset: he smiled at 6 months, sat unaided at 12 months, crawled at 18 months, walked at 3 years, and talked at 5 years of age. The EEG at age 7 years was abnormal, with excess slow waves, but he did not have overt epilepsy. At 15 years, his IQ was in the moderately retarded range and his behaviour was consistent with his mental age of 5½ years. At 14 years he functioned well socially, could

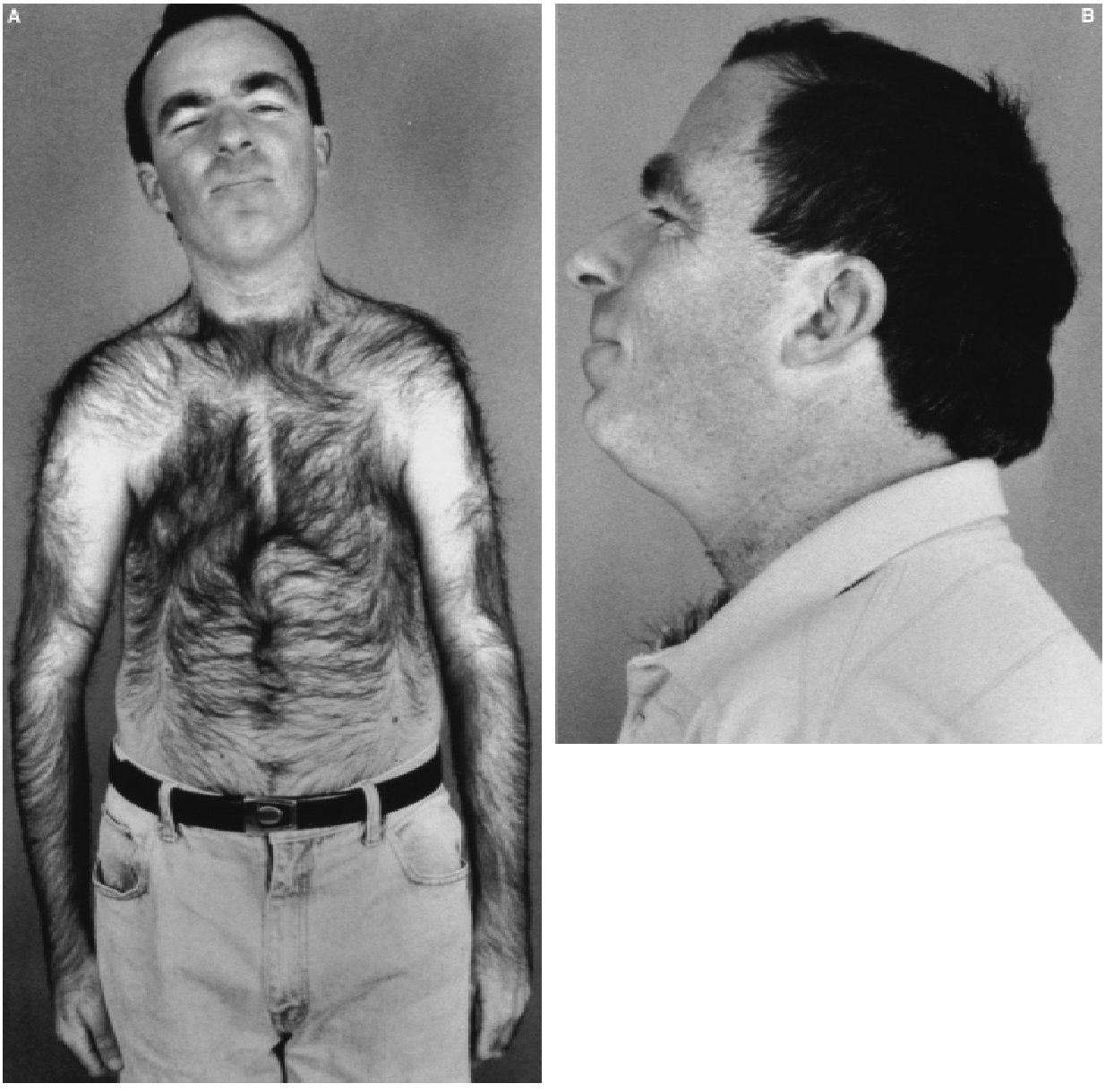

Fig. 1. The patient at 32 years. **A:** Front view. **B:** Lateral view. Note the bushy eyebrows and marked hirsutism.

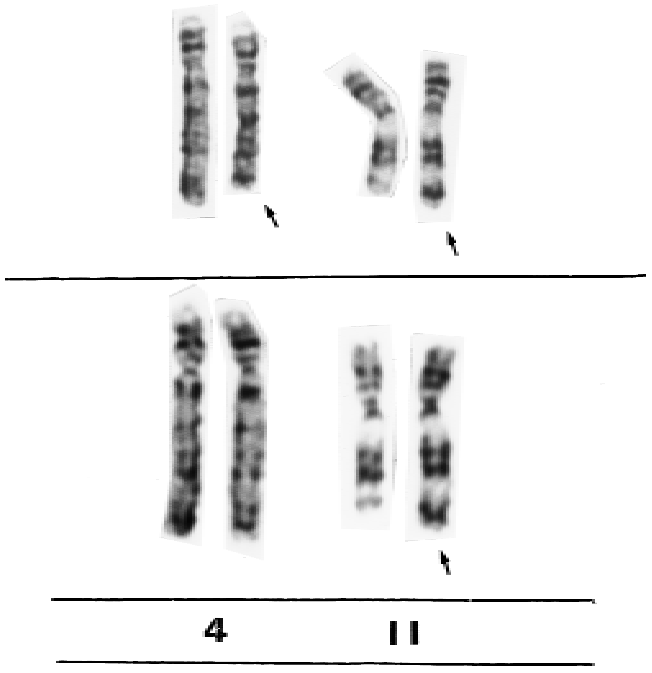

Fig. 2. Partial GTG banded karyotypes from the father, with balanced translocation **(top row)** and the patient, with unbalanced translocation **(bottom row).** The arrows indicate the derivative chromosomes.

travel alone to school by bus (three changes of bus route being involved), and could conduct appropriate conversation. At 32 years, his formal IQ was 52 (WISC). He functions well in a sheltered workshop and group home. Despite residual abnormalities of the feet, he walks to work and back each day independently.

CYTOGENETICS

Cytogenetic analysis in childhood with solid stain techniques was reported as normal—46,XY. Recent chromosome analysis with GTG banding showed an unbalanced translocation between 4q and 11q (Fig. 2). The extra material on chromosome 11 was too small to be detected without banding. Chromosome analysis of the parents showed that the father had a balanced translocation, 46,XY,t(4;11)(q32;q23.3) (Fig. 2). The karyotypes of the patient's 2 sibs showed the same balanced translocation as the father.

FISH Studies

Cells from the patient's sister, carrier of the balanced translocation, were analysed by fluorescence in situ hybridisation (FISH). The probes cAO353 and cE0182 were used. cA0353 is a cosmid probe which spans the region containing the rare folate sensitive fragile site FRA11B, the site of the deletion breakpoint for a small proportion of Jacobsen syndrome patients. cE0182 is a cosmid probe located distal to cA0353 [Jones et al., 1994]. Both of these probes were present on the normal and the derivative chromosome 11 in the balanced carrier, indicating that the translocation breakpoint was distal to the FRA11B region (Fig. 3).

DISCUSSION

Our patient has anomalies due to monosomy of distal 11q and trisomy of distal 4q. It is difficult to assign anomalies absolutely as deriving from one or the other imbalance. The cardiac anomalies, short stature, mental retardation, epicanthic folds, and "carp mouth" are reported in both imbalances and are not useful for phenotypic discrimination. Our patient has the bushy eyebrows described in trisomy 4q [Hustinx et al., 1993; Zollino et al., 1995]; this trait is not described in 11q–. His hirsutism began after the appearance of the bushy eyebrows noted at 15 years, so the hirsutism described in some cases of trisomy 4q may represent a phenotypic anomaly present with the ageing of these patients. Severe renal anomalies of the type present in our patient are most common in trisomy 4q, while the cryptorchidism and severe skeletal anomalies (particularly the feet) are most common in 11q–. Thus, our patient has signs of both imbalances [Angulo et al., 1984; Zollino et al., 1995; Penny et al., 1995] and individual anomalies of each syndrome as well.

Our patient is the oldest reported case of 11q– [Penny et al., 1995] and 4q+ [Zollino et al., 1995] and provides important data on the natural history of these 2 syndromes. While he had major problems in infancy and throughout childhood, requiring considerable medical care and hospitalisation, and has moderate in-

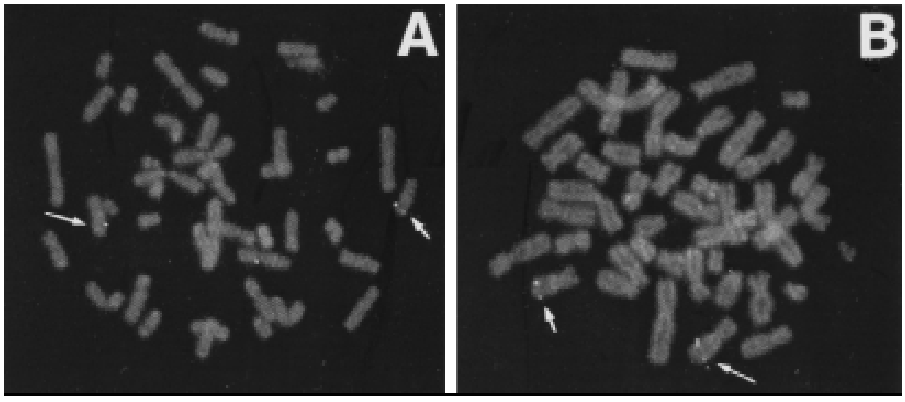

Fig. 3. Metaphases showing hybridisation of cAO353 **(A)** and cEO182 **(B)** to the chromosomes of the patient's sister (a balanced carrier). Hybridisation sites on the normal chromosome 11 are indicated by a small arrow and on the derivative chromosome 11 by a large arrow.

tellectual handicap, he functions well in a sheltered workshop and group home. His major health problem is due to slowly progressive renal disease, for which he is under a specialists care, and the hirsutism, which he finds embarrassing. Favourable long-term outcomes such as this need to be documented, to provide an overall perspective for genetic counselling after an abnormal result on prenatal diagnosis.

It is interesting that the breakpoint on the 11q has been associated with the fragile site at 11q23 [Voullaire et al., 1987; Jones et al., 1995]. Molecular studies of this region using a panel of localised probes have shown that a proportion of cases have breakpoints within 11q23.3, which may correlate with the rare folate sensitive fragile site—FRA11B [Penny et al., 1995]. Deletion breakpoint mapping has indicated that the clinical findings may divide into those due to deletion in the proximal part of the band and those due to deletion in the distal part. In our case, the breakpoint was outside the FRA11B region. This case provides another translocation to facilitate cloning of genes within the breakpoints of 4q and 11q, respectively.

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